Remarks

This Amendment was originally submitted by facsimile on 18 March 2003. As of 18 April 2003, the Examiner indicated that she had not received the earlier-faxed Amendment. The present Amendment is submitted in place of the one submitted on 18 March 2003, although it is substantially identical.

Please note that the attorney docket number for this application has changed and alter the Office's electronic records accordingly.

Claims 1-33, 47, and 48 are pending in the application. Claims 3 and 4 have been amended. Claims 1, 33, 47, and 48 are the only independent claims.

Claims 3 and 4 have been amended. No new matter is added by the amendments. Support for the amendments to these claims is found at least in note b on page 49 of the specification.

Each of the Examiner's objections or rejections is addressed below in the order they were presented in Paper No. 15.

I. Rejection Pursuant to 35 U.S.C. § 112, Second Paragraph

In items 5 and 6 of the Office Action, the Examiner rejects claims 3 and 4 because they recite an antibody designated "1B4" The Examiner notes that antibody is designated "IB4" in the ATCC hybridoma catalog and in U.S. Patent No. 5,147,637. The Examiner requests that "1B4" be changed to read "IB4" wherever it occurs in the application. The Applicant believes that this is unnecessary for at least three reasons.

First, the designations "1B4" and "IB4" are used interchangeably in the literature for this antibody. The following table summarizes references that refer to the antibody obtained from the hybridoma designated HB-10164 either as "1B4" or "IB4".

Refcrences Using "1B4"	References Using "IB4"
ID Labs Inc. Catalog No. IDAC1084	**ID Labs Inc. Catalog No. IDAC1084**
Horvath et al. 2002, Circ. Res. 90:488-494	**Horvath et al. 2002, Circ. Res. 90:488-494**
Filatove et al., 1990, Eksp. Onkol. 12(5):40-43	**Filatove et al., 1990, Eksp. Onkol. 12(5):40-43**
U.S. Patent Application 2002/0034765A1	U.S. Patent No. 5,147,637 *
Singer et al., 1993, J. Immunol. 150(7):2844-2857	ATCC Cell Lines and Hybridomas, 1994, p. 491 *
Seth et al., 1991, FEBS Lett. 282(1):193-196	Ancell Catalog No. 167-050
McDonald et al., 1993, Inflammation 17(2):145-151	
Web site of UK National Institute for Medical Research, "Search Selected Humanised Antibodies from the Literature" (also called "1B4" by the Examiner in the final Office Action - see items 9, 13, and 14)	* of record

The Applicant notes that the antibody is referred to both as "IB4" and as "1B4" in each of the three documents (highlighted) in the table. Because both designations are used in the literature to refer to the same antibody, the Examiner's preference for the designation not used by the applicants seems, at best, arbitrary. The Applicant respectfully contends that a skilled artisan understands that the antibody designated "1B4" in this application and elsewhere in the literature is the same antibody that is designated "IB4" in other examples in the literature. The used of both designations in the three highlighted references evidences the interchangeability of the designations to the skilled artisan.

Second, it is known in the art that the Arabic numeral "1" and the Roman numeral "I" both represent the number "one." Interchangeability of these two forms is well known.

Third, even if "1B4" were a designation made only by the Applicant in this application, the indication in note b on page 49 of the application suffices to indicate

to the skilled artisan that the antibody referred to is that secreted by the hybridoma having ATCC accession number HB-10164.

For the foregoing reasons, the Applicant respectfully contends that changing "IB4" to "IB4" throughout the application is unnecessary (and likely to introduce printing errors at the Patent Office). However, in order to assuage the Examiner's concerns with respect to claims 3 and 4, the Applicant has amended these two claims to recite "the antibody secreted by the hybridoma having ATCC accession no. HB-10164." The Applicant believes that this should overcome the Examiner's rejection. This amendment does not alter the scope or meaning of the claims.

For these reasons, the Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 3 and 4 pursuant to 35 U.S.C. § 112, second paragraph.

II. Claim Rejections Pursuant to 35 U.S.C. § 103(a)

In items 12-14 of the Office Action, the Examiner rejects claims 1-3, 5-33, 47, and 48 pursuant to 35 U.S.C. § 103(a) over Rogers in view of Waldmann, and claim 4 over Rogers in view of Waldmann and Wright. The Applicant respectfully contends that the Examiner is making a critical assumption that is not taught or suggested in any of the cited references.

The Examiner assumes that antibodies that bind specifically with CD18 will have the same effect on stenotic injury as antibodies raised against multimeric cell surface receptors that include a CD18 component. The Applicant has shown that this assumption is correct. However, the accuracy of this assumption was not know prior to when the Applicant's invention was made, and the Examiner's assumption must be considered in the context of a prior art-based rejection - WITHOUT using the benefit of hindsight and WITHOUT using information supplied by the Applicant to supplement what is taught in the prior art.

The Examiner's assumption is not supported by information that is prior art with respect to this application. Instead, the prior art taught the opposite - that CD18-

specific antibodies are not useful for the claimed methods. For this reason, the Examiner's assumption cannot be used to support a prior-art based rejection.

As noted in the Amendment submitted in response to the prior Office Action, i) neither the Rogers reference nor the Waldman reference teaches that antibodies that bind only with the CD18 portion of a leukocyte cell surface receptor is useful for inhibition or alleviation of stenotic injury and ii) the Guzman reference teaches that antibodies that bind specifically with the CD18 portion of leukocyte cell surface receptors were ineffective for preventing restenosis.

Viewed as a whole, the prior art not only fails to support the Examiner's assumption; instead, it teaches the opposite - that anti-CD18 antibodies are likely to be ineffective against stenotic injury.

In the final Office Action (see the portion of item 13 beginning with the fifth paragraph on page 5), the Examiner attempts to dismiss the teachings of the Guzman reference on at least three grounds: i) that Guzman predates Rogers, ii) that the procedures used by the Rogers and Guzman groups differed, and iii) that Rogers teaches or suggests use of an anti-CD18 antibody. The Applicant addresses each of these three issues in the ensuing three paragraphs.

The Examiner observes that Rogers (priority date March 1997) post-dates Guzman (published September 1995) by about 18 months. This is irrelevant. At no point does the Rogers publication indicate that the findings published in the Guzman reference are incorrect or unreliable. Both references stand on their own merits. Grossly simplified, Guzman teaches that anti-CD18 antibodies "don't work" for restenotic injury and Rogers teaches that antibodies against whole leukocyte cell surface receptors (which include CD18 and other subunits) "do work" for vascular injuries including restenotic injuries. A skilled artisan would NOT consider the Rogers and Guzman references incompatible and choose to ignore one or the other. Instead, the skilled artisan would consider both sets of observations compatible, and would conclude that an antibody effective for inhibiting restenotic injury MUST bind with either the binding partner (only) of CD18 or with both CD18 and its binding partner. Thus, the mere fact that Guzman

predates Rogers would not cause a skilled artisan to ignore the observations disclosed in Guzman.

The Examiner observes that the procedures used by the Guzman and Rogers groups differed. The Examiner indicates that the Guzman group administered anti-CD18 antibody at two time points, and that (in Example 2 of Rogers) the Rogers group administered an anti-Mac-1 antibody several times. The Examiner contends that a skilled artisan would ignore the findings of the Guzman group based on the differences in methodology. However, this contention is unsupported. Were the observations of Rogers and Guzman incompatible, a skilled artisan might assume that methodological differences accounted for the disparity. However, as noted above, the observations of the two groups are not incompatible. There is no evidence in either the Rogers or Guzman references that suggests that if the Guzman group had simply administered the anti-CD18 antibody more often or for a longer period, then results would have been obtained similar to those of Rogers. In the absence of such evidence, the Examiner is not permitted to simply ignore the teachings of Guzman. Neither is the Examiner permitted simply to assume that the methodologies used by Rogers are more appropriate than those used by Guzman. Furthermore, Rogers (see the sentence bridging pages 19 and 20) discloses that the time and duration of antibody administration is not critical. In view of these facts, there is no basis upon which the Examiner can justify simply ignoring Guzman based on purported inconsistencies in their methodologies.

The Examiner observes that Rogers teaches that several leukocyte cell surface receptors include a CD18 subunit. Rogers also teaches that antibodies raised against those receptors are useful for treating restenotic injury. However, Rogers is silent regarding what, if any, utility there might be for antibodies raised against CD18 (alone). Guzman is the only relevant prior art of record regarding the utility of such antibodies with regard to stenotic injury, and Guzman teaches the opposite of the Examiner's assumption. Rogers provides no support for the Examiner's assumption that anti-CD18 antibodies are useful for treatment of stenotic injury. The only evidence of record that such antibodies are useful for this purpose is the Applicant's disclosure. Another

reference by Rogers et al. (1998, Proc. Natl. Acad. Sci. USA 95:10134-10139, of record) indicates that antibodies raised against one beta-2-integrin (Mac-1), do not have the same effect as antibodies raised against two other beta-2 integrins (LFA-1 and p150,95). Those results also suggest that an antibody raised against a common portion (i.e., the CD18 subunit) of beta-2 integrins will not necessarily inhibit the activity of any of the integrins. The mere fact that Rogers (the PCT application) recognizes that CD18 is a subunit common to beta-2 integrins cannot be equated with recognition that an anti-CD18 antibody will inhibit the activity attributable to any beta-2 integrin. Thus, Rogers (the PCT application) does not teach or suggest any use for an anti-CD18 antibody.

For the reasons set forth in the preceding three paragraphs, the Applicant respectfully contends that the combined teachings of the Rogers and Guzman references cannot fairly be read to support the Examiner's assumption that anti-CD18 antibodies are useful for the claimed purposes.

As noted in the response to the previous Office Action, Waldmann discloses humanized anti-CD18 antibodies, but does not disclose or suggest that they can be used for inhibition or alleviation of stenotic injury. The Examiner contends that a skilled artisan having knowledge of the Rogers reference would be motivated to use the humanized anti-CD18 antibody disclosed in Waldmann because the humanized antibody would exhibit fewer complications. This analysis simply ignores the teachings of the Guzman reference. Guzman teaches that anti-CD18 antibodies are not useful for restenotic injury. A skilled artisan would not simply ignore the Guzman reference. In the absence of evidence to the contrary, a skilled artisan would assume, based on the Guzman reference, that the anti-CD18 antibody disclosed in Waldman (whether humanized or not) would be ineffective against stenotic injury. Nothing in either Rogers or Waldman discloses or suggests that anti-CD18 antibodies (or humanized anti-CD18 antibodies) exhibit the same utility as the anti-Mac-1 antibodies disclosed by Rogers.

For the foregoing reasons, the Applicant respectfully contends that the combined disclosures of Rogers and Waldman, considered in light of the state of the art

(Guzman) at the time the present application was filed, do not teach or suggest that an anti-CD18 antibody can be used to inhibit or alleviate stenosis in a human blood vessel.

The Examiner cites the Wright reference, together with the Rogers and Waldmann references, in support of the rejection of claim 4. The Examiner does not contend that Wright teaches that 1B4, or any other anti-CD18 antibody, is useful for inhibiting or alleviating stenosis. Thus, Wright does not overcome the deficiencies of Rogers and Waldmann.

For the foregoing reasons, the Applicant respectfully contends that no combination of the Rogers, Waldmann, and Wright references renders obvious any of the methods recited in claims 1-33, 47, and 48. Reconsideration and withdrawal of the rejections of these claims over Rogers in view of one or both of Waldmann and Wright are respectfully requested.

III. Summary

For the reasons set forth above, the Applicant respectfully contends that each of claims 1-33, 47, and 48 is in condition for allowance. Reconsideration and withdrawal of each of the Examiner's rejections are requested, and the Examiner is requested to issue a Notice of Allowance at the earliest possible time.

Respectfully submitted,

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(Date)

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Enclosures: Appendix A, listing references submitted herewith
References listed in Appendix A

Appendix A

ID Labs Inc. Catalog No. IDAC1084

Horvath et al. 2002, Circ. Res. 90:488-494

Filatov et al., 1990, Eksp. Onkol. 12(5):40-43 (abstract only)

U.S. Patent Application 2002/0034765A1 (relevant pages only)

Singer et al., 1993, J. Immunol. 150(7):2844-2857 (abstract only)

Seth et al., 1991, FEBS Lett. 282(1):193-196 (abstract only)

McDonald et al., 1993, Inflammation 17(2):145-151 (abstract only)

Web site of UK National Institute for Medical Research, "Search Selected Humanised Antibodies from the Literature"

Ancell Catalog No. 167-050